
## ATTACHMENT B

## REMARKS

By the present amendment, the claims have been rewritten in accordance with the Interview between Supervisor Tsang and Applicants' counsel so as to overcome the remaining rejection and to place this case in condition for allowance. In particular, the claims have been amended in the manner suggested by the Supervisor during the Interview, and information has been provided to show that the present invention is enabled for the entire scope of the claimed invention. The present amendments are clearly supported by the disclosure in all cases and no new matter has been added. In light of the present amendments to the claims and the arguments as set forth herein, as well as the citations provided herewith, Applicants submit that the present case is in condition for allowance for the reasons stated below.

As an initial matter, the Interview granted by Supervisory Examiner Tsang to Applicants' counsel is acknowledged with appreciation. During the Interview, the Supervisor reviewed the record of this application and agreed that Applicants had provided information and Declarations showing the activity and the effectiveness of the compounds of the Examples of the present application (e.g., in the Declarations filed January 22, 2003 and December 22, 2003, respectively), and that the activity of the compounds was associated with the symptoms of cognitive disorders such as Alzheimer's disease including attention, wakefulness and memory disorders (e.g., as shown in the Declaration filed June 4, 2004). However, the Supervisor's only remaining concern was that the supporting evidence may not have covered all of the aspects of the invention as claimed including all substituent elements of the various parts of the claim. Applicants have now complied with the Supervisor's request by amending the claim to cover embodiments exemplified in the Examples and shown to be

enabled as reflected in the detailed description below and accompanying references. In addition, the Supervisor indicated that the appropriate claim language should refer to a method of treating the symptoms associated with cognitive disorders (such as Alzheimer's disease), and Applicants have complied with this request as well. Accordingly, Applicant's amendments have placed this case in condition for allowance for the reasons as set forth in substantial detail below.

In the Official Action, the sole remaining rejection was on the basis that the subject matter of the claims was not described in the specification in such a way as to enable the full scope of the invention as claimed. However, during the Interview with the Supervisor, it was shown that Applicants had indeed pointed out that the claimed compounds have H3 receptor inhibitory activity throughout a wide range of examples and that there was a well established nexus between the symptoms of cognitive disorders and the inhibition of the H3 receptor. The Supervisor's only concern related to the possibility that some of the specific substituents in the prior claimed compounds were not reflected in the examples wherein the H3 receptor inhibitory activity had been shown.

Accordingly, in accordance with the Supervisor's concerns, Applicants have now amended the claims in such a manner as to be reflective of the examples which have been shown to have H3 receptor inhibitory activity in accordance with the present invention, and thus the invention is now shown to be enabled throughout all of the claimed compounds.

In order to make it clear that the present invention is enabled throughout the scope of the amended claims, a detailed analysis of the claimed compounds and activity of the exemplary examples, as well as a review of the relevant references reflecting work performed in this area, has been conducted as present below.

## 1. Analysis of the examples related to the amended general formula

### a. Analysis of the examples with regard to the nature of chain B" as described in the first set:

Chain B" is exemplified as aryl with chain A" being alkyl, X" being O and Y" being alkyl (ex #21) or aryl (ex #26).Compound of example 21 displays a Ki of 0.1 µM on rat H3 receptor and compound of example 26 shows a good brain availability as it has an ED50 of 2.8 mg/kg *per os* in a test measuring the level of tele-methylhistamine *in vivo* in mice.

| Ex N° | chain B" | NR1R2 | m | chain A" | X" | Y" |
|---|---|---|---|---|---|---|
| 21 | aryl | I | 4 | (CH2)5 | O | alkyl |
| 26 | aryl | I | 4 | (CH2)5 | O | phenyl |

Compound of example 21 displays a Ki of 0.1 µM on rat H3 receptor and compound of example 26 shows a good brain availability as it has an ED50 of 2.8 mg/kg *per os* in a test measuring the level of tele-methylhistamine *in vivo* in mice.

Chain B" as alkylene

chain B" is exemplified as a straight alkylene ranging from 1 to 3 with chain A" being an alkyl, X" being O and Y" being a branched alkylene with 5 carbon atoms (ex #115), an alkyl substituted with a phenyl (ex #116), an alkyl substituted with a substituted phenyl (ex #117), a phenyl (ex #144 145 146 147 148), a substituted phenyl (ex #149 150 151)

chain B" is exemplified as a straight alkylene ranging from 1 to 3 with chain A" being an alkyl, X" being OCONH and Y" being a straight alkyl (ex #120) or chain B" is a branched alkylene with the same values for chain A", X" and Y" (ex #121)

chain B" is exemplified as a straight alkylene ranging from 1 to 3 with chain A" being an alkyl, X" being NHCO and Y" being cycloalkyl (ex #125)

chain B" is also exemplified as a straight alkylene with chain A" being a saturated hydrocarbon chain interrupted by O (ex #115 120), in this case, chain B" can also be a branched alkylene chain (ex #121), or with chain A being a saturated hydrocarbon chain interrupted by NH (ex #125)



remarks

| Ex N° | chain B'' | R1, R2 | NR1R2 | m | Ra | chain A'' | X'' | Y'' |
|---|---|---|---|---|---|---|---|---|
| 148 | (CH2)3 | | i | 4 | | (CH2)3 | O | phenyl |
| 122 | (CH2)1 | | i | 5 | | (CH2)3 | SC(=NY''') NY'''' | substituted phenyl |
| 145 | (CH2)1 | | i | 5 | Me | (CH2)3 | O | phenyl |
| 167 | (CH2)1 | | i | 5 | | (CH2)3 | SC(=NY'') NHY'' | substituted phenyl |
| 120 | (CH2)1 | | i | 5 | | (CH2)3O | CONH | Straight alkyl 4C |
| 125 | (CH2)2 | | i | 4 | | (CH2)3NH | CO | cycloalkyl 5 |
| 115 | (CH2)2 | | i | 5 | | (CH2)3 | O | branched alkyl 4C |
| 144 | (CH2)2 | | i | 5 | Me | (CH2)3 | O | phenyl |
| 146 | (CH2)2 | | i | 5 | Me | (CH2)3 | O | phenyl |
| 149 | (CH2)2 | | i | 5 | Me | (CH2)3 | O | substituted phenyl |
| 170 | (CH2)3 | Et Et | | | | (CH2)3 | O | phenyl |
| 121 | branched alkyl C2 | | i | 5 | | (CH2)3 | OCONH | branched alkyl 4C |
| 116 | (CH2)3 | | i | 5 | | (CH2)3 | O | Phenyl |
| 117 | (CH2)3 | | i | 5 | | (CH2)3 | O | Substituted phenyl |
| 146 | (CH2)3 | | i | 5 | Me | (CH2)3 | O | Phenyl |
| 150 | (CH2)3 | | i | 5 | Me | (CH2)3 | O | Substituted phenyl |
| 151 | (CH2)3 | | i | 5 | Me | (CH2)3 | O | Substituted phenyl |
| 120 | (CH2)3 | | i | 5 | | (CH2)3O | CONH | straight alkyl 2C |
| 121 | branched alkyl C5 | | i | 5 | | (CH2)3 | OCONH | straight alkyl 1C |

These compounds are good H3 ligands on the human receptor as compounds of examples 148, 116, 117, 144, 146, 151 and 167 display affinities of 3.9, 7.0, 2.4, 47, 15*, 18 and 132 nM respectively.

(*N-methylhistamine was used instead of iodoproxyfan as ligand)



remarks

Other compounds have been evaluated as ligands on the rat receptor and compounds of examples 122 and 144 display affinities of 481 and 34 nM respectively.
Moreover, they show a good brain bioavailability in the measure of tele-methylhistamine *in vivo* in mice, as compounds of examples 116, 117, 145, 146, 149 and 151 display ED50s of 3.7, 1.6, 8.9, 8.7, 2.8 and 12 mg/kg *per os* respectively.

**b. Analysis of the examples with regard to the nature of chain B" as described in the second set.**

Chain B" can be selected from lower alkyl with chain A" also being a lower alkyl.
With this set of value, X" can be O and Y" represents a phenyl group (ex #116, 145, 146, 147, 148, 170)

| Ex N° | chain B" | R1, R2 | NR1R2 | m | Ra | chain A" | X" | Y" |
|---|---|---|---|---|---|---|---|---|
| 147 | (CH2)1 | | i | 5 | Me | (CH2)3 | O | phenyl |
| 170 | (CH2)2 | Et Et | | | | (CH2)3 | O | phenyl |
| 116 | (CH2)3 | | i | 5 | | (CH2)3 | O | phenyl |
| 146 | (CH2)3 | | i | 5 | Me | (CH2)3 | O | phenyl |
| 148 | (CH2)3 | | i | 4 | | (CH2)3 | O | phenyl |

These compounds are good H3 ligands on the human receptor as compounds of examples 147, 116 and 148 display affinities of 18, 7 and 3.9 nM respectively.
Some of these compounds have also been evaluated as ligands on the rat receptor and compounds of examples 147 and 116 display affinities of 18 and 15 nM respectively.
Moreover, they show a good brain bioavailability in the measure of tele-methylhistamine *in vivo* in mice, as compounds of examples 146, 147, 116 and 148 display ED50s of 8.7, 9.3, 3.7 and 5.5 mg/kg *per os* respectively.

With this set of value, X" can be O or -SC(=NY")NY"- and Y" represents a substituted phenyl (ex #117, 122, 149, 150, 151 and 167)



remarks

| Ex N° | chain B" | NR1R2 | m | Ra | chain A" | X" | Y" |
|---|---|---|---|---|---|---|---|
| 122 | (CH2)1 | i | 5 | | (CH2)3 | SC(=NY"')NY"" | substituted phenyl |
| 150 | (CH2)1 | i | 5 | Me | (CH2)3 | O | substituted phenyl |
| 167 | (CH2)1 | i | 5 | | (CH2)3 | -SC(=N"')NHY""- | substituted phenyl |
| 149 | (CH2)2 | i | 5 | Me | (CH2)3 | O | substituted phenyl |
| 151 | (CH2)2 | i | 5 | Me | (CH2)3 | O | substituted phenyl |
| 117 | (CH2)3 | i | 5 | | (CH2)3 | O | substituted phenyl |

These compounds are good H3 ligands on the human receptor as compounds of examples 117, 149 and 151 display affinities of 2.4, 51 and 18 nM respectively.
Some of these compounds have also been evaluated as ligands on the rat receptor and compounds of examples 117, 122 and 149 display affinities of 17, 481 and 64 nM respectively. Moreover, they show a good brain bioavailability in the measure of tele-methylhistamine *in vivo* in mice, as compounds of examples 117, 149, 150 and 151display ED50s of 1.6, 2.8, 20 and 12 mg/kg *per os* respectively.

With this set of value, X" can be O, or OCONH and Y" represents a straight or branched alkyl (ex #115, 120, 121)

| Ex N° | chain B" | NR1R2 | m | chain A" | X" | Y" |
|---|---|---|---|---|---|---|
| 115 | (CH2)2 | I | 5 | (CH2)3 | O | branched alkyl 4C |
| 120 | (CH2)3 | I | 5 | (CH2)3 | OCONH | straight alkyl 1C |
| 121 | branched alkyl C5 | I | 5 | (CH2)3 | OCONH | straight alkyl 1C |

Some of these compounds have also been evaluated as ligands on the rat receptor and compound of example 115 displays an affinity of 0.29 µM.

With this set of value, X" can be O and Y" represents an alkyl substituted with phenyl (ex #116) or with substituted phenyl (ex #117)



remarks

| Ex N° | chain B" | NR1R2 | m | chain A" | X" | Y" |
|---|---|---|---|---|---|---|
| 116 | (CH2)1 | i | 5 | (CH2)3 | O | alkyl substituted with phenyl |
| 117 | (CH2)1 | i | 5 | (CH2)3 | O | alkyl substituted with substituted phenyl |

These compounds have both been evaluated as ligands of the human H3 receptor and display an affinity of 7 and 2.4 nM respectively. They are also efficient in an in vivo test in mice measuring the level of tele-methylhistamine. The display ED50s of 3.7 and 1.6 mg/kg *per os* respectively.

Chain B" can be selected from lower alkyl interrupted by an heteroatom with chain A" also being a lower alkyl.
With this set of value, X" can be alkyl and Y" represents a phenyl group

| Ex N° | chain B" | R1, R2 | NR1R2 | m | Ra | p, q, r | chain A" | X" | Y" |
|---|---|---|---|---|---|---|---|---|---|
| 1 | CH2O | | i | 5 | | | CH2 | (CH2)3 | phenyl |
| 3 | CH2O | | Me<br>Et | | | | CH2 | (CH2)3 | phenyl |
| 4 | CH2O | | morpholino | | | | (CH2)3 | CH2 | phenyl |
| 10 | CH2O | | i | 5 | Me | | (CH2)3 | CH2 | phenyl |
| 11 | CH2O | | piperazino<br>R=alcanoyl | | | | CH2 | (CH2)3 | phenyl |
| 12 | CH2O | | i | 5 | Me | | CH2 | (CH2)3 | phenyl |
| 13 | CH2O | | i | 5 | Me | | (CH2)3 | CH2 | phenyl |
| 15 | CH2O | | i | 5 | carbalcox<br>y | | (CH2)2 | (CH2)2 | phenyl |
| 28 | CH2O | | i | 4 | | | CH2 | (CH2)3 | phenyl |
| 29 | CH2O | | ii | | | 1, 1, 1 | (CH2)2 | (CH2)2 | phenyl |
| 35 | CH2O | | i | 4 | | | CH2 | CH2 | phenyl |
| 5 | (CH2)2O | | i | 6 | | | CH2 | (CH2)2 | phenyl |



remarks

| Ex N° | chain B" | R1, R2 | NR1R2 | m | Ra | p, q, r | chain A" | X" | Y" |
|---|---|---|---|---|---|---|---|---|---|
| 6 | (CH2)2O | Et<br>Pr | | | | | (CH2)2 | CH2 | phenyl |
| 7 | (CH2)2O | | i | 5 | Me | | (CH2)2 | CH2 | phenyl |
| 8 | (CH2)2O | | i | 5 | Pr | | CH2 | (CH2)2 | phenyl |
| 9 | (CH2)2O | | i | 5 | Me | | CH2 | (CH2)2 | phenyl |
| 14 | (CH2)2O | | i | 5 | Me | | (CH2)2 | CH2 | phenyl |
| 16 | (CH2)2O | | i | 5 | Carb-alcoxy | | CH2 | (CH2)2 | phenyl |
| 17 | (CH2)2O | | ii | | | 1, 2, 1 | CH2 | (CH2)2 | phenyl |
| 26 | (CH2)2O | | i | 4 | | | CH2 | (CH2)2 | phenyl |
| 31 | (CH2)2O | | i | 4 | | | CH2 | CH2 | phenyl |
| 33 | CH2S | | i | 4 | | | (CH2)2 | (CH2)2 | phenyl |
| 34 | CH2S | | i | 4 | | | CH2 | (CH2)2 | phenyl |
| 32 | (CH2)4O | | i | 4 | | | CH2 | CH2 | phenyl |
| 136 | (CH2)2NH | | i | 5 | | | (CH2)3 | CH2 | phenyl |

Some of these compounds have been evaluated as ligands on the rat receptor and compounds of examples 10, 12, 13, 5, 6, 7, 9, 14 and 17 display affinities of 29, 90, 95, 115, 460, 99, 93, 115, 252 nM respectively.

Moreover, they show a good brain bioavailability in the measure of tele-methylhistamine *in vivo* in mice, as compounds of examples 1 and 26 display ED50s of 6.9 and 2.8 mg/kg *per os* respectively.

With this set of value, X" can be alkyl and Y" represents a substituted phenyl group

| Ex N° | chain B" | R1, R2 | NR1R2 | m | Ra | p, q, r | chain A" | X" | Y" |
|---|---|---|---|---|---|---|---|---|---|
| 19 | CH2O | | i | 4 | | | (CH2)3 | CH2 | substituted phenyl |



remarks

| Ex N° | chain B" | R1, R2 | NR1R2 | m | Ra | p, q, r | chain A" | X" | Y" |
|---|---|---|---|---|---|---|---|---|---|
| 22 | CH2O | | i | 4 | | | CH2 | (CH2)3 | substituted phenyl |
| 25 | CH2O | | i | 4 | | | CH2 | (CH2)3 | substituted phenyl |
| 26 | CH2O | | i | 4 | | | (CH2)2 | (CH2)2 | substituted phenyl |
| 27 | CH2O | | i | 4 | | | (CH2)2 | (CH2)2 | substituted phenyl |
| 30 | CH2O | | i | 4 | | | (CH2)2 | (CH2)2 | substituted phenyl |
| 40 | CH2O | | i | 4 | | | (CH2)2 | (CH2)2 | substituted phenyl |
| 41 | CH2O | | i | 4 | | | (CH2)2 | (CH2)2 | substituted phenyl |
| 42 | CH2O | Me Et | | | | | CH2 | CH2 | substituted phenyl |
| 43 | CH2O | Et Et | | | | | CH2 | CH2 | substituted phenyl |
| 45 | CH2O | | i | 4 | | | (CH2)2 | (CH2)2 | substituted phenyl |
| 46 | CH2O | Et Et | | | | | CH2 | CH2 | substituted phenyl |
| 47 | CH2O | | i | 4 | | | CH2 | (CH2)3 | substituted phenyl |
| 50 | CH2O | | i | 4 | | | (CH2)2 | (CH2)2 | substituted phenyl |
| 53 | CH2O | Me Me | | | | | (CH2)3 | CH2 | substituted phenyl |
| 55 | CH2O | Me Me | | | | | CH2 | CH2 | substituted phenyl |
| 58 | CH2O | | i | 4 | | | CH2 | CH2 | substituted phenyl |
| 59 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 60 | CH2O | | i | 6 | | | CH2 | CH2 | substituted phenyl |
| 62 | CH2O | Pr Pr | | | | | CH2 | CH2 | substituted phenyl |
| 63 | CH2O | Et Et | | | | | CH2 | CH2 | substituted phenyl |
| 64 | CH2O | Et Et | | | | | CH2 | CH2 | substituted phenyl |
| 65 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 66 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 67 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |



remarks

| Ex N° | chain B'' | R1, R2 | NR1R2 | m | Ra | p, q, r | chain A'' | X'' | Y'' |
|---|---|---|---|---|---|---|---|---|---|
| 68 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 69 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 70 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 71 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 72 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 73 | CH2O | Et Et | | | | | CH2 | CH2 | substituted phenyl |
| 74 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 75 | CH2O | | ii | | | 1, 2, 1 | CH2 | CH2 | substituted phenyl |
| 76 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 77 | CH2O | | i | 5 | | | CH2 | branched alkylene C2 | substituted phenyl |
| 78 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 79 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 80 | CH2O | | i | 5 | | | CH2 | branched alkylene C2 | substituted phenyl |
| 81 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 82 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 83 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 84 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 85 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 86 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 87 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 88 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 89 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 90 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 91 | CH2O | | i | 5 | Me Et | | CH2 | CH2 | substituted phenyl |



remarks

| Ex N° | chain B" | R1, R2 | NR1R2 | m | Ra | p, q, r | chain A" | X" | Y" |
|---|---|---|---|---|---|---|---|---|---|
| 93 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 94 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 95 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 96 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 97 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 98 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 99 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 100 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 101 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 102 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 103 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 104 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 105 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 106 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 107 | CH2O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 108 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 109 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 110 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 111 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 112 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 113 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 114 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 160 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 161 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |



remarks

| Ex N° | chain B" | R1, R2 | NR1R2 | m | Ra | p, q, r | chain A" | X" | Y" |
|---|---|---|---|---|---|---|---|---|---|
| 162 | CH2O | | i | 5 | | | CH2 | CH2 | substituted phenyl |
| 18 | (CH2)2O | | i | 4 | | | (CH2)2 | CH2 | substituted phenyl |
| 20 | (CH2)2O | | i | 4 | | | CH2 | (CH2)2 | substituted phenyl |
| 21 | (CH2)2O | | i | 4 | | | (CH2)2 | CH2 | substituted phenyl |
| 28 | (CH2)2O | | i | 4 | | | (CH2)2 | CH2 | substituted phenyl |
| 48 | (CH2)2O | | i | 4 | | | (CH2)2 | CH2 | substituted phenyl |
| 49 | (CH2)2O | | i | 4 | | | CH2 | (CH2)2 | substituted phenyl |
| 51 | (CH2)2O | Et Et | | | | | CH2 | (CH2)2 | substituted phenyl |
| 52 | (CH2)2O | | i | 5 | | | (CH2)2 | CH2 | substituted phenyl |
| 56 | (CH2)2O | Et Et | | | | | CH2 | (CH2)2 | substituted phenyl |
| 61 | (CH2)2O | Et Et | | | | | (CH2)3 | CH2 | substituted phenyl |
| 36 | (CH2)3O | | i | 4 | | | CH2 | CH2 | substituted phenyl |
| 37 | (CH2)3O | | i | 4 | | | CH2 | CH2 | substituted phenyl |
| 38 | (CH2)3O | | i | 5 | Me | | CH2 | CH2 | substituted phenyl |
| 39 | (CH2)3O | | i | 4 | | | CH2 | CH2 | substituted phenyl |
| 57 | (CH2)3O | Pr Pr | | | | | CH2 | CH2 | substituted phenyl |

These compounds are good H3 ligands on the human receptor as compounds of examples 22, 26, 38, 39, 50, 52, 58, 59, 60, 67, 68, 69, 70, 72, 74, 76, 81, 83, 85, 86, 87, 88, 89, 90, 95, 96, 97, 100, 101, 102, 104, 111, 112, 113, 114, 160, 161 and 162 display affinities of 9.0*, 19*, 7.0*, 7.0*, 17, 20, 5.0*, 6.9, 4.1*, 1.2, 16, 5.0, 7.0*, 3.2, 4.5, 3.8, 2.6, 5.0*, 14*, 5.0*, 16, 3.4, 3.6, 2.3, 8.0*, 2.0, 16, 6.7*, 0.66*, 2.6*, 9.7, 14, 6.9, 8.1, 12, 0.09, 0.53 and 0.42 nM respectively.

(*with N-methyl-histamine as ligand)

Some of these compounds have also been evaluated as ligands on the rat receptor and compounds of examples 18, 20, 21, 22, 36, 37, 38, 39, 40, 41, 46, 49, 50, 52, 58, 60, 61, 62,



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63, 64, 65, 67, 68, 69, 70, 74, 76, 77, 78, 81, 83, 88, 89, 94, 95, 100, 101 and 102 display affinities of 39, 53, 112, 19, 103, 113, 14, 19, 100, 73, 20, 26, 28, 25, 20, 8.7, 53, 134, 60, 2.7, 6.0, 1.8, 4.6, 4.7, 5.1, 7.6, 3.6, 47, 37, 8.2, 10, 4.5, 9.9, 6.0, 11, 6.8, 2.5 and 4.9 nM respectively.

Moreover, they show a good brain bioavailability in the measure of tele-methylhistamine *in vivo* in mice, as compounds of examples 18, 19, 22, 37, 38, 39, 40, 42, 43, 45, 46, 47, 49, 50, 51, 52, 56, 58, 59, 60, 61, 63, 64, 65, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 81, 82, 83, 84, 86, 87, 88, 89, 90, 91, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113 and 114 display ED50s of 1.1, 7.3, 1.9, 5.1, 1.3, 1.5, 2.6, 1.5, 0.5, 3.6, 0.44, 2.0, 1.7, 1.0, 3.0, 2.0, 1.1, 1.6, 0.2, 0.64, 4.2, 0.45, 0.73, 1.1, 0.08, 0.49, 0.6, 3.5, 4.2, 0.5, 0.47, 0.2, 2.2, 0.18, 0.77, 0.36, 0.61, 1.3, 0.78, 0.53, 0.82, 1.6, 0.14, 1.3, 0.59, 1.7, 0.85, 1.8, 2.6, 0.83, 1.5, 4.5, 3.4, 0.39, 0.17, 2.1, 2.3, 0.3, 3.4, 4.0, 2.5, 3.3, 3.1, 2.4, 0.92, 1.6, 0.54 and 1.2 mg/kg *per os* respectively.

With this set of value, X" can be an alkyl group and Y" represents an alkyl (ex #115)

| Ex N° | chain B" | NR1R2 | m | chain A" | X" | Y" |
|---|---|---|---|---|---|---|
| 115 | CH2O | i | 5 | (CH2)2 | CH2 | branched alkyl 6C |

With this set of value, X" can be an alkyl group and Y" represents a biphenyl (ex #26 and 28) or a benzophenone (ex #44).

| Ex N° | chain B" | NR1R2 | m | chain A" | X" | Y" |
|---|---|---|---|---|---|---|
| 28 | (CH2)2O | i | 4 | (CH2)2 | CH2 | Diphenyl |
| 26 | (CH2)3O | i | 4 | CH2 | CH2 | Diphenyl |
| 44 | (CH2)2O | i | 4 | CH2 | (CH2)2 | Benzophenone |

Some of these compounds are efficient H3 antagonists and show a good brain bioavailability in the measure of tele-methylhistamine *in vivo* in mice, as compounds of examples 26 and 44 display ED50s of 2.8 and 4.4 mg/kg *per os* respectively.



remarks

With this set of value, X" can be an alkyl group and Y" represents an heterocycle with one nitrogen atom (ex #133, 134, 135, 163, 164 and 165) or a benzene fused with an heterocycle (ex #118, 152, 154, 159, 166 and 168) or an heterocycle with two nitrogen atom (ex #135)

| Ex N° | chain B" | NR1R2 | m | chain A" | X" | Y" |
|---|---|---|---|---|---|---|
| 133 | (CH2)2NH | i | 5 | (CH2)3 | CH2 | substituted heterocycle N |
| 134 | (CH2)2NH | i | 5 | (CH2)2 | (CH2)2 | substituted heterocycle N |
| 163 | (CH2)2NH | i | 5 | CH2 | (CH2)2 | substituted heterocycle N |
| 164 | (CH2)2NH | i | 5 | (CH2)2 | CH2 | substituted heterocycle N |
| 165 | (CH2)2NH | i | 5 | CH2 | (CH2)2 | substituted heterocycle N |
| 135 | (CH2)3NH | i | 5 | (CH2)2 | CH2 | substituted heterocycle 2N |
| 152 | (CH2)4NH | i | 5 | CH2 | CH2 | fusion benzene to heterocycle N |
| 118 | CH2O | i | 5 | CH2 | CH2 | fusion benzene to heterocycle N S |
| 168 | (CH2)4NH | i | 5 | CH2 | CH2 | fusion benzene to heterocycle N S |
| 154 | (CH2)2NH | i | 5 | (CH2)2 | (CH2)2 | fusion benzene to heterocycle N substituted |
| 156 | (CH2)2NH | i | 5 | CH2 | CH2 | fusion benzene to heterocycle N substituted |
| 157 | (CH2)2NH | i | 5 | (CH2)5 | CH2 | fusion benzene to heterocycle N substituted |
| 158 | (CH2)2NH | i | 5 | (CH2)7 | CH2 | fusion benzene to heterocycle N substituted |
| 159 | (CH2)2NH | i | 5 | (CH2)6 | (CH2)4 | fusion benzene to heterocycle N substituted |
| 166 | (CH2)2NH | i | 5 | (CH2)2 | (CH2)2 | fusion benzene to heterocycle N substituted |

These compounds are good H3 ligands on the human receptor as compounds of examples 152, 154, 156, 157, 159 and 166 display affinities of 7.6, 3.6, 82, 7.8, 32 and 26 nM respectively.

Some of these compounds have also been evaluated as ligands on the rat receptor and compounds of examples 118, 133, 134, 135 and 165 display affinities of 96, 30, 10, 95 and 44 nM respectively.



remarks

Moreover, they show a good brain bioavailability in the measure of tele-methylhistamine *in vivo* in mice, as compounds of examples 118, 133 and 163 display ED50s of 18, 3.8 and 2.7 mg/kg *per os* respectively.

With this set of value, X" can be an alkyl group and Y" represents a naphtyl (ex #23 and 24) or polyhydronaphtyl (ex #27 and 30).

| Ex N° | chain B" | NR1R2 | m | chain A" | X" | Y" |
|---|---|---|---|---|---|---|
| 23 | CH2O | i | 4 | CH2 | (CH2)3 | naphtyl |
| 24 | CH2O | i | 4 | (CH2)3 | CH2 | naphtyl |
| 27 | (CH2)2O | i | 4 | (CH2)2 | CH2 | tetrahydronaphtyl |
| 30 | (CH2)3O | i | 4 | CH2 | CH2 | tetrahydronaphtyl |

Some of these compounds are efficient H3 antagonists and show a good brain bioavailability in the measure of tele-methylhistamine *in vivo* in mice, as compounds of examples 23 and 27 display ED50s of 4.5 and 6.6 mg/kg *per os* respectively.

With this set of value, X" can be an alkyl group and Y" represents a phenyl alkyl ketone (ex #39, 44, 45, 46, 65, 66, 67, 68, 69, 70, 72, 73, 74, 75, 76, 77, 88, 89, 90, 94, 95, 101 and 102)

| Ex N° | chain B" | R1, R2 | NR1R2 | m | Ra | p, q, r | chain A" | X" | Y" |
|---|---|---|---|---|---|---|---|---|---|
| 69 | CH2O | | i | 5 | | | CH2 | CH2 | C6H4COCH2CH3 |
| 73 | CH2O | Et Et | | | | | CH2 | CH2 | C6H4COCH2CH3 |
| 88 | CH2O | | i | 5 | Me | | CH2 | CH2 | C6H4COCH2CH3 |
| 94 | CH2O | | i | 5 | Me | | CH2 | CH2 | C6H4COCH2CH3 |
| 95 | CH2O | | i | 5 | Me | | CH2 | CH2 | C6H4COCH2CH3 |
| 72 | CH2O | | i | 5 | | | CH2 | CH2 | C6H4COCH(CH3)2 |
| 74 | CH2O | | i | 5 | | | CH2 | CH2 | C6H4CO(CH2)2CH3 |



remarks

| Ex N° | chain B" | R1, R2 | NR1R 2 | m | Ra | p, q, r | chain A" | X" | Y" |
|---|---|---|---|---|---|---|---|---|---|
| 45 | CH2O | | i | 4 | | | CH2 | (CH2) 3 | C6H4COCH2Ph |
| 39 | CH2O | | i | 4 | | | CH2 | (CH2) 3 | C6H4COCH3 |
| 46 | CH2O | Et Et | | | | | CH2 | CH2 | C6H4COCH3 |
| 65 | CH2O | | i | 5 | | | CH2 | CH2 | C6H4COCH3 |
| 66 | CH2O | | i | 5 | Me | | CH2 | CH2 | C6H4COCH3 |
| 67 | CH2O | | i | 5 | Me | | CH2 | CH2 | C6H4COCH3 |
| 68 | CH2O | | i | 5 | Me | | CH2 | CH2 | C6H4COCH3 |
| 70 | CH2O | | i | 5 | Me | | CH2 | CH2 | C6H4COCH3 |
| 75 | CH2O | | ii | | | 1, 2, 1 | CH2 | CH2 | C6H4COCH3 |
| 77 | CH2O | | i | 5 | | | CH2 | branch ed alkyle ne C2 | C6H4COCH3 |
| 80 | CH2O | | i | 5 | | | CH2 | branch ed alkyle ne C2 | C6H4COCH3 |
| 89 | CH2O | | i | 5 | | | CH2 | CH2 | C6H4COcyclobutyl |
| 90 | CH2O | | i | 5 | | | CH2 | CH2 | C6H4COcyclopentyl |
| 76 | CH2O | | i | 5 | | | CH2 | CH2 | C6H4COcyclopropyl |
| 101 | CH2O | | i | 5 | Me | | CH2 | CH2 | C6H4COcyclopropyl |
| 102 | CH2O | | i | 5 | Me | | CH2 | CH2 | C6H4COcyclopropyl |
| 44 | (CH2)2 O | | i | 4 | | | (CH2)2 | CH2 | C6H4COPh |

These compounds are good H3 ligands on the human receptor as compounds of examples 39, 65, 66, 67, 69, 72, 74, 76, 88, 89, 90, 95, 101 and 102 display affinities of 7.0*, 6.3, 1.3*, 1.2, 5.0, 3.2, 4.5, 3.8, 3.4, 3.6, 2.3, 8.0*, 0.66*, 2.6* nM respectively.

Some of these compounds have also been evaluated as ligands on the rat receptor and compounds of examples 46, 65, 66, 67, 69, 70, 73, 75, 76, 88, 89, 94 and 101 display affinities of 20, 6.0, 3.7, 1.8, 4.7, 5.1, 11, 7.3, 3.6, 4.5, 9.9, 6.0 and 2.5 nM respectively.



remarks

Moreover, they show a good brain bioavailability in the measure of tele-methylhistamine *in vivo* in mice, as compounds of examples 39, 44, 45, 46, 65, 66, 67, 68, 69, 70, 72, 73, 74, 75, 76, 88, 89, 90, 94, 95, 101 and 102 display ED50s of 1.5, 4.4, 3.6, 0.44, 1.1, 0.34, 0.08, 0.49, 0.6, 3.5, 0.5, 0.47, 0.21, 2.2, 0.18, 0.14, 1.3, 0.59, 1.8, 2.6, 0.17 and 2.1 mg/kg *per os* respectively.

With this set of value, X" can be an alkyl group and Y" represents a phenyl alcohol (ex #50, 63, 96 and 97)

| Ex N° | chain B" | R1, R2 | NR1R2 | m | Ra | chain A" | X" | Y" |
|---|---|---|---|---|---|---|---|---|
| 50 | CH2O | | i | 4 | | (CH2)3 | CH2 | C6H4CHOHCH3 |
| 63 | CH2O | Et Et | | | | CH2 | CH2 | C6H4CH(OH)CH3 |
| 96 | CH2O | | i | 5 | Me | CH2 | CH2 | C6H4CH(OH)CH2CH3 |
| 97 | CH2O | | i | 5 | Me | CH2 | CH2 | C6H4CH(OH)CH2CH3 |

Some of these compounds are efficient H3 antagonists and show a good brain bioavailability in the measure of tele-methylhistamine *in vivo* in mice, as compounds of examples 50, 63, 96 and 97 display ED50s of 1.0, 0.45, 0.83 and 1.5 mg/kg *per os* respectively.

Y" as a substituted phenyl is exemplified the substituent being nitro (ex #18 and 36) halogen (ex #19, 25, 37, 82 and 108) Oalkyl (ex #20) straight or branched alkyl (ex #21, 111, 112, 113 and 114) alkene (ex #104) CHO (ex #71) ketone (ex #39, 44, 45, 46, 65, 66, 67, 68, 69, 70, 72, 73, 74, 75, 76, 77, 80, 81, 88, 89, 90, 94, 95, 101, 102 and 162) oxime (ex #98 107 and 64) O-alkyloxime (ex #99 and 105) aldehyde (ex #71) SO2NMe2 (ex #110) alcohol (ex #50, 63, 96 and 97)

These compounds are good H3 ligands on the human receptor as compounds of examples 39, 50, 65, 66, 67, 69, 72, 74, 76, 81, 88, 89, 90, 96, 111, 112, 113 and 162 display affinities of 7.0*, 17, 6.3, 1.3*, 1.2, 5.0, 3.2, 4.5, 3.8, 2.6, 3.4, 3.6, 2.3, 2.0, 14, 6.9, 8.1 and 0.42 nM respectively.

Some of these compounds have also been evaluated as ligands on the rat receptor and compounds of examples 20, 21, 25, 36, 37, 39, 46, 50, 64, 65, 66, 67, 68, 69, 70, 73, 74, 76,



remarks

88, 94, 101 and 102 display affinities of 53, 112, 209, 103, 113, 19, 20, 28, 2.7, 6.0, 3.7, 1.8, 4.6, 4.7, 5.1, 11, 7.6, 3.6, 4.5, 6.0, 2.5 and 4.9 nM respectively.
Moreover, they show a good brain bioavailability in the measure of tele-methylhistamine *in vivo* in mice, as compounds of examples 18, 19, 37, 39, 44, 45, 46, 50, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 81, 82, 88, 89, 90, 94, 95, 96, 97, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 112, 113 and 114 display ED50s of 1.1, 7.3, 5.1, 1.5, 4.4, 3.6, 0.44, 1.0, 0.45, 0.73, 1.1, 0.34, 0.08, 0.49, 0.6, 3.5, 4.2, 0.5, 0.47, 0.21, 2.2, 0.18, 0.61, 1.3, 0.14, 1.3, 0.59, 1.8, 2.6, 0.83, 1.5, 4.5, 3.4, 0.17, 2.1, 0.3, 3.4, 2.5, 3.3, 2.4, 0.92, 1.6, 0.54 and 1.2 mg/kg *per os* respectively.

Y" as an optionally substituted aryl group includes all the examples of the preceding paragraph, but also some other substituted phenyl such as those of examples 40, 47, 49, 103, 106 and 160.
Some of these compounds are efficient H3 antagonists and show a good brain bioavailability in the measure of tele-methylhistamine *in vivo* in mice, as compounds of examples 40, 47, 49, 103 and 106 display ED50s of 2.6, 2.0, 1.7, 2.3 and 4.0 mg/kg *per os* respectively. Compound #160 is a good H3 ligand on the human receptor as it displays an affinity of 0.09 nM on this receptor.

i) m=3 has been prepared more recently with chain A" being an alkyl, X" being oxygen, chain B" being alkyl and Y" being a phenyl substituted with a halogen.
iv') Y" representing indanyl has been prepared more recently with chain A" being alkyl, X" being CH2 and chain B" as CH2O
iii') chain B" as unsaturated lower alkyl (alkyne) has been used in US2004/0002604 (pub 20040101)
Various other substituted piperazines as NR1R2 have been disclosed in US6,559,140 (pub 2003/05/06)
Y" as substituted phenyl alcohol has been published very recently WO 2002076925 with NR1R2=piperidine instead of diethylamine in our example 63 and other close analogs.



remarks

## 2. The compounds belonging to the claims show $H_3$ histamine receptor antagonistic activity

As reflected in the information as described below, the compounds as defined by the present claims and specifically the formula of Claim 1 possess the claimed antagonistic activity.

**a)** In the first place, the present specification contained several examples where the antagonistic activity was quantified, and this information was supplemented by the several Declarations filed in conjunction with this application.

In particular, significant antagonistic activity (ED50 expressed in mg/kg) was shown for at least 88 compounds exemplified in the specification (see Declaration under Rule 132 by Jean-Charles Schwartz dated December 19, 2003 and filed December 22, 2003). In addition, this antagonist activity is related to an unexpected general mechanism. Even further, it was known that a very large number of classes of imidazole compounds show such activity. This is stated in the specification (see for example page 1, lines 20-32 of the specification).

**b)** Since the application of the present invention, many other imidazole compounds acting on the histamine $H_3$ receptor were developed and patented. A non exhaustive list of such further developments on imidazole compounds having activity on the $H_3$ receptor is given here below.

- Histamine H3 receptor ligands, WO 9729092, 1997-08-14, James Black Foundation
- Histamine H3 receptor ligands, WO 9905141, 2000-03-29, James Black Foundation
- 1H-4(5)-substituted imidazole derivatives, their preparation and their use as histamine H3 receptor ligands, US 6355665, 2002-03-12, James Black Foundation
- Substituted imidazoles, their preparation and use, WO 0042023, 2000-07-20, Bohringer Novo Nordisk
- Substituted imidazoles, their preparation and use, WO0063208, 2000-10-26, Bohringer Novo Nordisk
- Piperidyl-imidazole derivatives, their preparations and therapeutic uses, WO 0064884, 2000-11-02, Bohringer Novo Nordisk
- Imidazo heterocyclic compounds, US 2001049385, 2001-12-06, Bohringer Novo Nordisk
- Imidazole compounds, US 2002058659, 2002-05-16, Bohringer Novo Nordisk



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- Substituted imidazoles, their preparation and use, US6417218, 2002-07-09, Bohringer Novo Nordisk
- Condensed imidazoles as histamine H3 receptor ligands, WO 0168652, 2003-01-02, Bohringer Novo Nordisk
- Condensed imidazoles as histamine H3 receptor ligands, WO 0168651, 2003-01-02, Bohringer Novo Nordisk
- Preparation and use of substituted imidazoles, WO 03040106, 2003-05-15, Bohringer Novo Nordisk
- Imidazole compounds, US 2003135056, 2003-07-17, Bohringer Novo Nordisk
- Substituted imidazoles, US 2004127718, 2004-07-01, Bohringer Novo Nordisk
- Method of stimulating histamine H3-receptors, US 5047418, 1991-09-10, Glaxo
- S-(3-(4(5))-imidazolyl)propyl)isothiourea as selective trhistomine H3 receptor antagonist, WO 9301812, 1993-02-04, Glaxo
- Histamine H3-receptor antagonists and therapeutic uses thereof, WO 9511894, 1995-05-04, Gliatech
- Histamine H3-receptor antagonists and therapeutic uses thereof, US5486526, 1996-01-23, Gliatech
- 1h-4(5)-substituted imidazole derivatives, WO 9638142, 1996-12-05, Gliatech
- 2-(1h-4(5)-imidazoyl) cyclopropyl derivatives, WO 9638141, 1996-12-05, Gliatech
- 1h-4(5)-substituted imidazole derivatives, WO 9640126, 1996-12-19, Gliatech
- 2-(4-imidazoyl) cyclopropyl derivatives, US 5652258, 1997-07-29, Gliatech
- 2-(1H-4(5)-imidazoyl) cyclopropyl compounds, US 5990317, 1999-11-23, Gliatech
- 2-(1H-4(5)-imidazoyl) cyclopropyl derivatives, US 6008240, 1999-12-28, Gliatech
- 1H-4(5)-cyclo-substituted imidazole derivatives as histamine H3 receptor agents, US 6072057, 2000-06-06, Gliatech
- Chiral imidazoyl intermediates for the synthesis of 2-(4-imidazoyl)-cyclopropyl derivatives, WO 0181317, 2001-11-01, Gliatech
- Chiral imidazoyl intermediates for the synthesis of 2-(4-imidazoyl)-cyclopropyl derivatives, US2001047100, 2001-11-29, Gliatech
- Novel alicyclic imidazoles as H3 agents, WO 0213821, 2002-02-21, Gliatech



remarks

- The use of histamine H3 receptor inverse agonists for the control of appetite and treatment of obesity, WO 0215905, 2002-02-28, Gliatech
- Novel alicyclic imidazoles as H3 agents, US 2002042400, 2002-04-11, Gliatech
- 1H-4(5)-substituted imidazole derivatives, US 6448282, 2002-09-10, Gliatech
- Histamine H3 receptor ligands, WO 9729092, 1997-08-14, James Black Foundation
- Histamine H3 receptor ligands, WO 9905141, 1999-02-04, James Black Foundation
- Substituted imidazole derivatives and their use as histamine H3 receptor ligands, WO 9905115, 1999-02-04, James Black Foundation
- 1h-4(5)-substituted imidazole derivatives, their preparation and their use as histamine H3 receptor ligands, WO 9905114, 1999-02-04, James Black Foundation
- Sulfonamides and sulfamides as H3 receptor antagonists, US 6080871, 2000-06-27, James Black Foundation
- Substituted imidazole derivatives and their use as histamine H3 receptor ligands, US6407132, 2002-06-18, James Black Foundation
- Imidazolyl derivatives useful as histamine H3 receptor ligands, WO 02079168, 2002-10-10, Johnson and Johnson Ortho McNeil
- Heterocyclic compounds, US 2002198237, 2002-12-26, Johnson and Johnson Ortho McNeil
- Heterocyclic compounds, US 2004147577, 2004-07-29, Johnson and Johnson Ortho McNeil
- Novel alicylic imidazoles as H3 agents, US 2004029943, 2004-02-12, Merck
- Alicyclic imidazoles as H3 agents, US 6794405, 2004-09-21, Merck
- Histamine receptor antagonists, US 2004138234, 2004-07-15, Pfizer
- Aminoalkylimidazole derivatives, particularly 4-[□-(2, 5-dihydropyrrol-1-yl)alkyl]-1H-imidazole derivatives, and their preparation and therapeutic use as H3 histamine receptor antagonists for the treatment of obesity, diabetes, and other conditions, WO 2003011856, 2004-02-13, Sanofi
- Imidazolyl-alkyl-piperazine and -diazepine derivatives as histamine H3 agonists/antagonists, WO 9312093, 1993-06-24, Schering
- Imidazolyl-alkyl-piperazine and -diazepine derivatives as histamine H3 agonists/antagonists., EP 0618905, 1994-10-12, Schering



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- Phenyl-alkyl-imidazoles as H3 receptor antagonists, WO 9924406, 1999-05-20, Schering
- H3 receptor ligands of the phenyl-alkyl-imidazoles type, WO 9924405, 1999-05-20, Schering
- H3 receptor ligands of the phenyl-alkyl-imidazoles type, US 5990147, 1999-11-23, Schering
- N-(imidazolylalkyl)substituted cyclic amines as histamine-H3 agonists or antagonists, WO 0023438, 2000-04-27, Schering
- Imidazole compounds substituted with a six or seven membered heterocyclic ring containing two nitrogen atoms, WO 0053596, 2000-09-14, Schering
- N-(imidazolylalkyl)substituted cyclic amines as histamine-H3 agonists or antagonists, US 6133291, 2000-10-17, Schering
- Imidazole compounds substituted with a six or seven membered heterocyclic ring containing two nitrogen atoms, US 6211182, 2001-04-03, Schering
- Imidazole compounds as histamine H3 ligands, EP1159275, 2001-12-05, Schering
- Substituted imidazoles as dual histamine H1 and H3 agonists or antagonists, WO0224659, 2002-03-28, Schering
- Substituted imidazoles as dual histamine H1 and H3 agonists or antagonists, WO 0244141, 2002-06-06, Schering
- Substituted imidazoles as dual histamine H1 and H3 agonists or antagonists, US 2002082272, 2002-06-27, Schering
- Substituted imidazoles as dual histamine H1 and H3 agonists or antagonists, US 2002086859, 2002-07-04, Schering
- Substituted imidazoles as dual histamine H1 and H3 agonists or antagonists, US 2002103235, 2002-08-01, Schering
- Substituted imidazoles as dual histamine H1 and H3 agonists or antagonists, US6506756, 2003-01-14, Schering
- Substituted imidazoles as dual histamine H1 and H3 agonists or antagonists, US6518287, 2003-02-11, Schering
- Substituted imidazoles as dual histamine H1 and H3 agonists or antagonists, US6528522, 2003-03-04, Schering



remarks

- Substituted imidazoles as dual histamine H1 and H3 agonists or antagonists, US 6762186, 2004-07-13, SCHERING
- 4-[4'-piperidinyl or 3'-pirrolidinyl] substituted imidazoles as H3-receptor antagonists and therapeutic uses thereof, WO9320061, 1993-10-14, Univ. Toledo (US)
- Histamine H3-receptor antagonists and therapeutic uses thereof, US5633382, 1997-05-27, Univ. Toledo (US)
- 4-[4'-piperodinyl or 3'-pirrolidinyl] substituted imidazoles as H3-receptor antagonists and therapeutic uses thereof, US 5639775, 1997-06-17, Univ. Toledo (US)
- Imidazole-derivatives having agonistic or antagonistic activity on the histamine H3-receptor, WO 9215567, 1992-09-17, Vrije Universiteit
- Imidazole-derivatives having antagonistic activity on the histamine H3-receptor, EP 0573542, 1993-12-15, Vrije Universiteit
- New imidazole derivatives having agonistic or antagonistic activity on the histamine H3 receptor, WO 9506037, 1995-03-02, Vrije Universiteit
- Imidazole-derivatives having agonistic or antagonistic activity on the histamine H3-receptor, US 5837718, 1998-11-17, Vrije Universiteit.

Accordingly, it is now accepted that the presence of the imidazole ring is very prevalent for this H3 histamine receptor activity which allows to use compounds having many different structures linked to the imidazole group.

The inventors discovered that it was also possible to keep this activity by replacing the imidazole group by the $NR_1R_2$ groups as defined in the specification and more restrictively in the main claim. They also discovered that such replacement suppressed or dramatically lowered toxicity of the already known imidazole compounds and that it was possible to use the discovered compounds for treating symptoms and illnesses such as, for example, the symptoms and illnesses recited in the claim. Accordingly, it is clear that the structure of the $NR_1R_2$ group is prevalent in contributing to the claimed activity and uses.

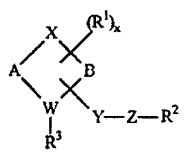
**c)**. This general property was now confirmed by a large number of patents and publications by third parties after the filing and publication of the present invention. The following citations are



remarks

patent publications for general formula and/or specific compounds which correspond to or overlap with the general formula for the compounds according to the present main claim. These compounds show histamine H3 receptor antagonistic or related activity.

▪ Histamine H3 receptor ligands, EP 1056733, 2000-12-06, James Black Foundation



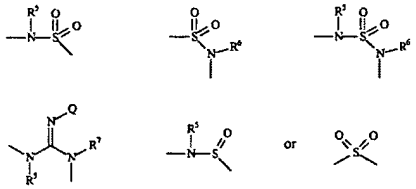
A is $(CH_2)_m$, m being from 1 to 3; $R^2$ is H or $C_1$ to $C_{15}$ hydrocarbyl, in which up to 3 carbon atoms may be replaced by O, S or N, and up to 3 hydrogen atoms may be replaced by halogen;

B is $(CH_2)_n$, n being from 1 to 3;

W is nitrogen;

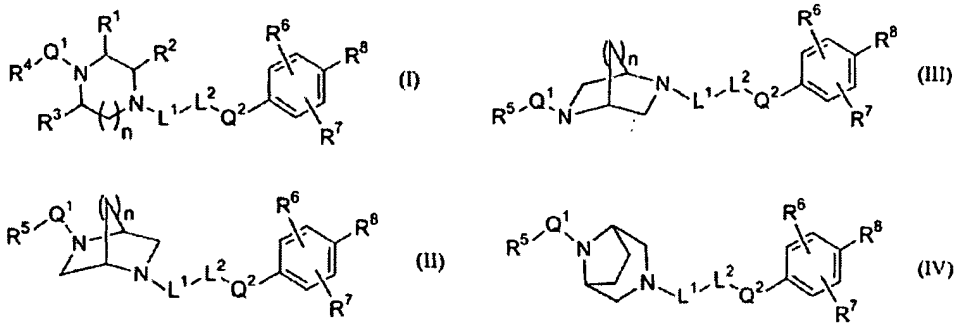
X is $-CH_2-$, -O- or $-NR^4-$, $R^4$ being H or $C_1$ to $C_3$ alkyl;

Y replaces a hydrogen atom on any of A, B, W and X, and is $C_2$ to $C_{10}$ alkylene, in which one non-terminal carbon atom may be replaced by O; and Z is



When Y-Z-R2 is on W (which is nitrogen), there is an analogy with our general formula (IX) or (X), as W-A-X-B corresponds to a cyclised NR1R2, Y corresponds to chain $X^{ix}_{mix}$ or alkylene, Z correspond to the sulfamide or sulfonylureas and R2 to $R1^{IX}$ or $R2^{X}$

▪ Cyclic and bicyclic diamino histamine-3 receptor antagonists, WO 0166534, 2001-09-13, Abbott

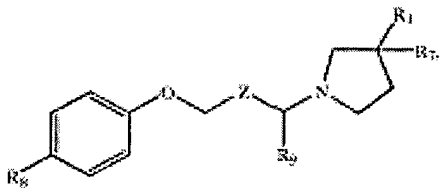


This general formula corresponds to our formula (IIa) with NR1R2 as a bicyclic or tricyclic diamine. Some of the piperazine derivatives are encompassed by the claims of the present application.

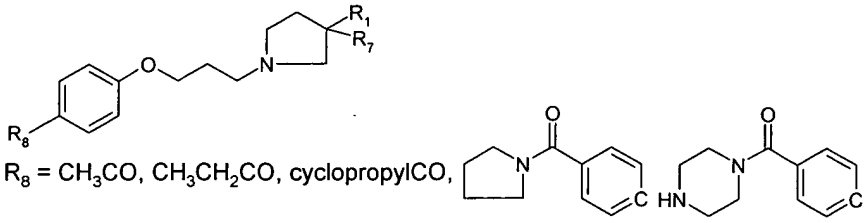


remarks

▪ 1,3-Disubstituted and 1,3,3-trisubstituted pyrrolidines as histamine-3 receptor ligands and their therapeutic applications, US 2002035103, 2002-03-21, Abbott

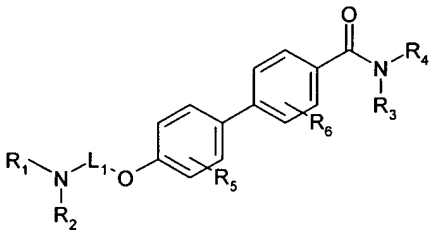


The exemplified compounds all fall into the following restricted formula:



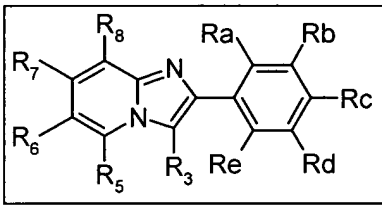

This part is clearly analogous to many of the examples of the present invention.

▪ Aminoalkoxybiphenyl carboxamides as histamine-3 receptor ligands and their therapeutic applications, WO 0240461, 2002-05-23, Abbott



This formula is clearly encompassed by general formula (IIa) of the claims with chain A" as alkylene, X" as oxygen, chain B" as phenyl and Y" as substituted phenyl. Moreover biphenyl ethers have been exemplified (ex 26 and 28) in the present application.

▪ Phenyl-substituted imidazopyridines, WO 0174815, 2001-10-11, Johnson and Johnson Ortho McNeil

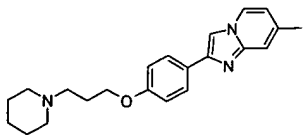
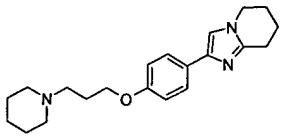
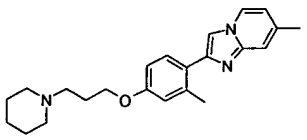
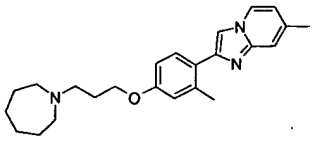
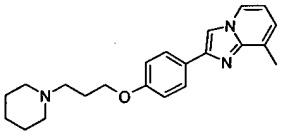


one of Ra, Rb, Rc, Rd, Re is WYZ
W is -O-, alcoxy, alkylamino ...
Y is absent or alkylene ...
Z is C2-8 heterocylic radical... with at least one basic N



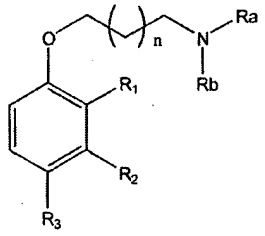
remarks

The definition of WYZ has a great overlap with the general formula of the claims of the present invention. The examples with the best affinities are the following:

| Ex | Structure | Ki (nM) |
|---|---|---|
| 8 |  | 1 |
| 16 |  | 0,75 |
| 22 |  | 1 |
| 24 |  | 0,5 |
| 54 |  | 1 |

These examples are very close to the definition of formula (IIa) with chain A" as 'hydrocarbon chain', X" as oxygen, chain B" as 'aryl' and Y" as ' a bicyclic radical resulting from the fusion of a benzene ring to a heterocycle '.

▪ Non-imidazole aryloxyalkylamines as h3 receptor ligands, WO 2002012214, 2002-02-14, Johnson and Johnson Ortho McNeil



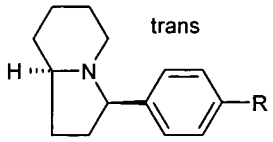

This general formula is clearly very close to formula (IIa) or (I).



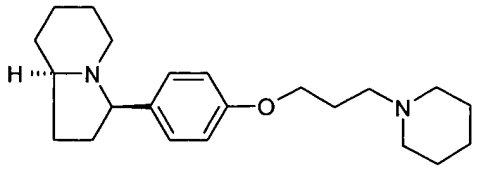
remarks

▪ Octahydro-indolizine and quinolizine and hexahydro-pyrrolizine, WO 0224695, 2002-03-28, Johnson and Johnson Ortho McNeil

All the exemplified compounds of this patent fall into this general formula:

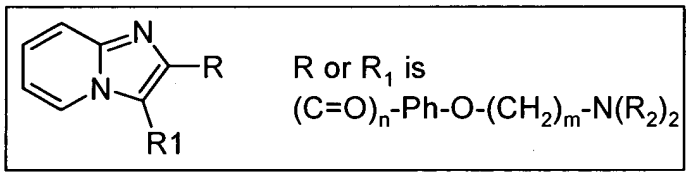



The product showing the best affinity among the exemplified compounds is the following:

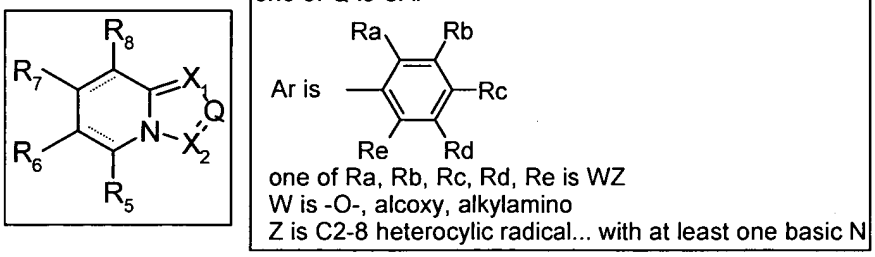



This demonstrates, once again, that the pharmacophore is well described by the general formula of the claims of the present application.

▪ Method for treating histamine H3 receptor-mediated disorders with 2- or 3-aryl substituted imidazo[1, 2-a] pyridines, US 6489337, 2002-12-03, Johnson and Johnson Ortho McNeil



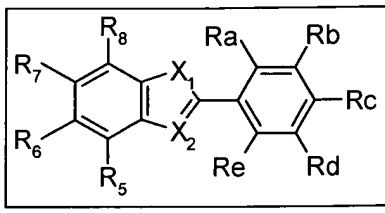

▪ Phenyl-substituted indolizine derivatives and their use as histamine H3 ligands, WO 0174814, 2003-01-02, Johnson and Johnson Ortho McNeil




▪ Phenyl-substituted indoles as histamine H3-receptor antagonists, WO 0174773, 2003-01-02, Johnson and Johnson Ortho McNeil

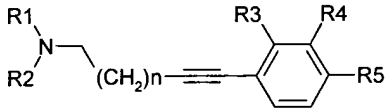


remarks



one of Ra, Rb, Rc, Rd, Re is WZ
W is -O-, alcoxy, alkylamino
Z is C2-8 heterocylic radical... with at least one basic N

- Phenylalkynes, US 2004002604, 2004-01-01, Johnson and Johnson Ortho McNeil

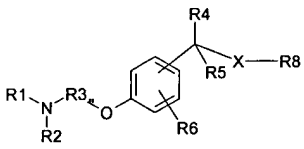


One of R2, R3, R4 is G
and the others are H, C1-C3alkoxy, halogen, CF3, CH3, NO2

G : L2Q — L2 : méthylene
Q est généralement N — piperidine, Aniline...

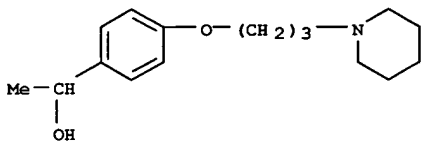
n : 0, 1

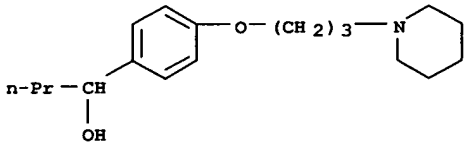
- Non-imidazole aryl alkylamines compounds as histamine H3 receptor antagonists, preparation and therapeutic uses, WO 02076925, EP1379493, 2004-01-14, Eli Lilly



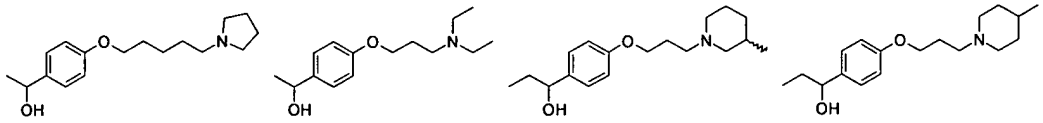
X : O, NR7, S
R1 : H, alkyl, cycloalkyl, aryl, heteroaryl
R2 : COR1 ou cyclisé pour avec R1 pour faire une cycle a 4, 5 ou 6 (avec heteroatomes ou CO, cycle pouvant etre substitué une ou deux fois par un alkyl en C1-C4)
R3 : cycloalkylene ou alkylene
R4 : H, halo, alkyl, cycloalkyl, aryl, heteroaryl,CO, cyclisé avec R5 (cyclopropane)
R5 : H, alkyl
R6 : H, halo, cyclisé avec R5 (cycle a 5 ou 6), cyclisé avec R7 (heterocycle à 5 ou 6)
R7 : H, alkyl (substitué ou pas par halogène), cycloalkyle, aryl, heteraryl, SO2R1, cyclisé avec R8 ( cycle à 5, 6, 7 substitué ou pas )
R8 : H, alkyl, bond, SO2R9, CO2R10, COR9, CONHR10

This general formula has a broad overlap with the claims of the present application. Moreover, specific examples such as the following:





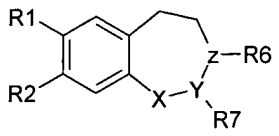
are very close to some of the compound exemplified in our patent (50, 63, 96 and 97)



- Substituted azepines as histamine H3 receptor antagonists, preparation and therapeutic uses, WO 2004018432, 2004-03-04, Eli Lilly



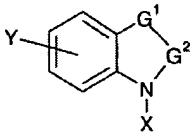
remarks



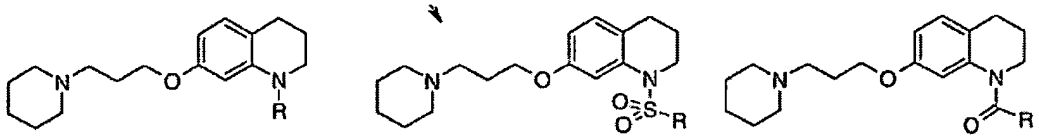

| | |
|---|---|
| R1 et R2 : | sont indépendamment H, OR3NR4R5 (un seul est OR3NR4R5) |
| R3 : | alkylene |
| R4 : | alkyl |
| R5 : | alkyl ou cyclisé avec R4 pour former piperidinyl ou pyrrolidinyl |
| X : | CH2 ou CO |
| Y, Z : | CH2 ou N (un seul des deux est N) |
| R6 : | H, alkyl, CH2Ph, CO2R, SO2R, CONHR, COR, CH2CH2NRR |
| R7: | idem R6 |

With R1 or R2 as OalkyleneNR4R5, these compounds correspond to formula (IIa) with chain A" as '-(CH2)nII-', Y", chain B" as ' -(CH2)nII(hetero atom)- where the hetero atom is preferably a sulphur or oxygen' and as Y" ' a phenyl ring fused to a heterocycle comprising a nitrogen hetero atom '

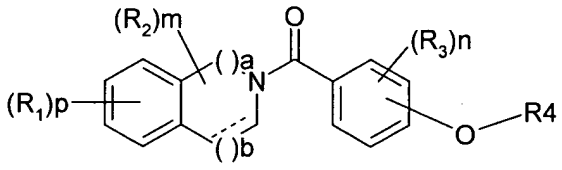
- Histamine H3 receptor antagonists, preparation and therapeutic uses, WO 2004026837, 2004-04-01, Eli Lilly




Here again, the value of Y corresponding to the group R1R2N-chainA"-X"-chainB", there is an overlap with the present claims. The general scheme of synthesis clearly shows that such compounds correspond to formula (IIa) with chain A" as '-(CH2)nII-', Y", chain B" as ' -(CH2)nII(hetero atom)- where the hetero atom is preferably a sulphur or oxygen' and as Y" ' a phenyl ring fused to a heterocycle comprising a nitrogen hetero atom '




- Substituted piperazines, (1, 4) diazepines, and 2, 5-diazabicyclo (2.2.1) heptanes as histamine H1 and/or H3 antagonists or histamine H3 reverse antagonists, WO 2004035556, 2004-04-29, Glaxo

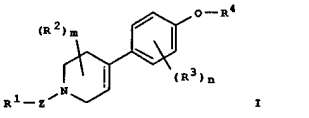



As R4 represent an alkylene bearing an amine that can be cyclic or not, these compounds are closely related to the present claims.

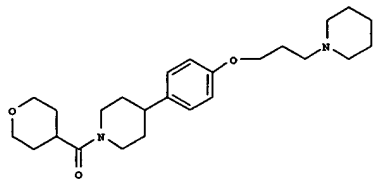


remarks

▪ 4- (4-(heterocyclylalkoxy}phenyl)-1-(heterocyclyl-carbonyl)piperidine derivatives and related compounds as histamine H3 antagonists for the treatment of neurological diseases such as Alzheimer's, WO 2004089373, 2004-10-21, Glaxo



I



II

These compounds are clearly closely related to the numerous basic phenol ether disclosed in the present application.

Many other later patent publications disclose general formulae or compounds which are close to the general formula or compounds of the claims of the present application.

These documents confirm that with a $NR_1R_2$ group according to the claimed invention, there is a very high probability that using compounds having the chain A"-X"-chain B"-Y" structure have an antagonistic activity on the histamine $H_3$ receptor.

In the specification, it is clearly mentioned that "*antagonist and/or agonist compounds can be obtained by substituting a di(alkyl) or (cycloalkyl)amine or a non-aromatic nitrogen-containing ring -NR1R2 as above-defined for the imidazole ring, in known antagonist and/or agonist imidazole derivatives*".

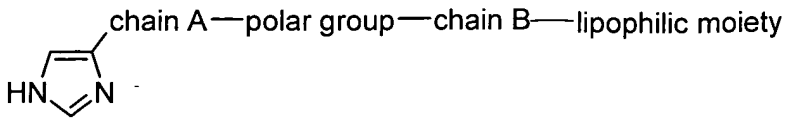
Some examples were clearly shown in table IV of the specification, other are easily inferred from the examples and the well-known imidazole ligands of the H3 receptor.

This comparative list was also published[1].

The commonly accepted pharmacophore of the imidazole containing ligands before the priority dates was the following:



remarks




This scheme was completed by a publication revealing that the polar group could be replaced by a lipophilic moiety[1].

In its general definition (main claims of the application and priority applications as initially filed), the invention teaches that imidazole moiety can be replaced, and the pharmacological properties improved by a definition of the amine NR1R2, and the group W recites the different values that were known to give H3 ligands when attached to an imidazole. These different values of W have been exemplified with different values of the amine moiety and shown to give non-imidazole H3 ligands. This is also consistent with the above-mentioned commonly accepted wide pharmacophore of the imidazole ligands.

The intention of replacement of imidazole by basic amine has been recognised as sound as many publications presenting this concept have been accepted in peer-reviewed publications[2,3,4,5].

Moreover, acknowledgment of this invention has also been published recently by two independent groups.

The first one states[6]: "*This series of analogs incorporates the same tail group as ciproxifan so it appears that the piperazine amide may be acting as a surrogate for the imidazole ring.*" Monoacylated amine fits into the values proposed for NR1R2, moreover, this is exemplified in the present application (ex. 11).

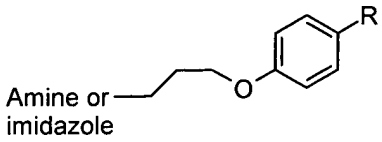
The second one makes the following picture for known H3 ligands[7]:

---

[1] H. Stark et al., Bioorg. Med. Chem. Lett. (1998) 8 2011-2016.
[2] G. Meier et al., Eur. J. Pharm. Sci. (2001) 13 249-259.
[3] G. Meier et al., Bioorg. Med. Chem. (2002) 10 2535-2542.
[4] J. Apelt et al., J. Med. Chem. (2002) 45 1128-1141.
[5] T. Miko et al., Bioorg. Med. Chem. (2004) 2727-2736.
[6] R. Aslanian, N.-Y. Shih, Ann. Rep. Med. Chem (2004) 39 57-66.
[7] M. Cowart et al., Bioorg. Med. Chem. Lett. (2004) 14 689-693.



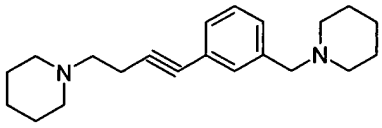
remarks



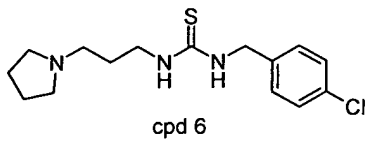

This picture clearly shows that the amine can replace the imidazole moiety in the field of the H3 ligands.

The replacement of imidazole for piperidine is not restricted to ether containing compounds.

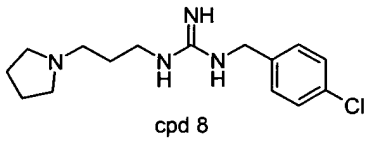
This has been exemplified for the non-imidazole compounds such as compound of example 136. This idea has been further exploited by another group and led to the following compound[8].



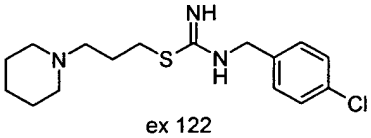

Another publication[9] is closely related to other of the linkers according to the invention as can be seen in the following scheme:



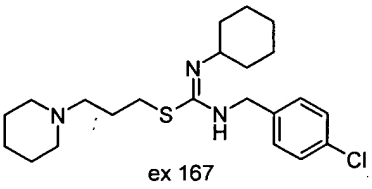

cpd 6




cpd 8




ex 122




ex 167

The general formula (IIa) of the present application describes a very useful scheme for preparing ligands of the H3 receptor. This formula has been pointed out by several independent different groups.

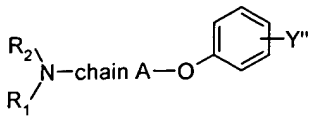
When X" is an oxygen and chain B" is an aryl, the formula is the following:

---

[8] WO 2003/050099.
[9] I.D. Linney et al., J. Med. Chem. (2000) 43 2362-2370.



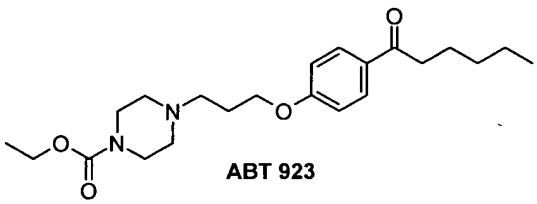
remarks



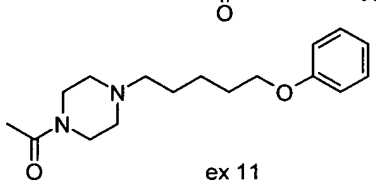
This general formula with chain A as a three methylene unit is "*the amino-propyloxy-aryl combination seen in compounds 5-7* [which] *may represent a privileged H3 antagonist pharmacophore*"[7]. It also corresponds to "*we chose to retain the piperidinopropyloxyphenyl fragment which is optimal according to our previous results. This piperidinopropyloxyphenyl fragment is also present in the potent non-imidazole H3 described by other groups*[10]". The other groups mentioned in this last citation refer to the inventor's work.1

It is thus not surprising that many compounds acting as ligands at the H3 receptor are very close to some of the examples of the specification.

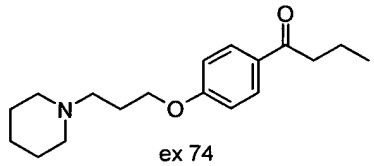
Such comparison can be obviously seen between A-923[11] and ex. 11 or 74.



ABT 923

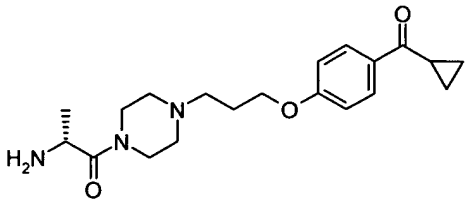


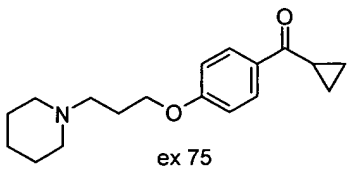
ex 11



ex 74

This compound has been derived into a cyclopropyl ketone[12] looking like ex. 75, but with the aminoacid appendage onto the piperazine.





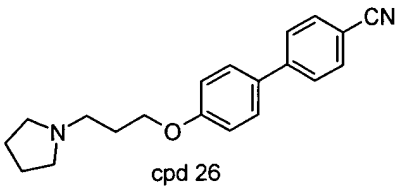
ex 75

Other work led to biphenylnitrile[13] which are related to some of our examples.

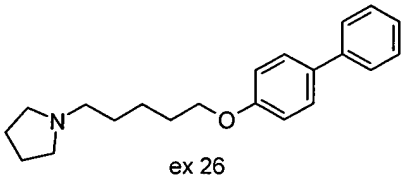
[10] W. Chai et al., Bioorg. Med. Chem. Lett. (2003) 13 1767-1770.
[11] R. Faghih et al., Bioorg. Med. Chem. Lett. (2002) 12 2031.
[12] G.B. Fox et al., J. Pharmacol. Exp. Ther. (2003) 305 897.
[13] R. Faghih et al., Bioorg. Med. Chem. Lett. (2002) 12 3077.



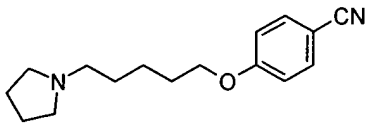
remarks




cpd 26



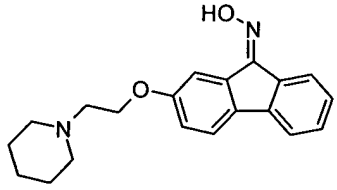

ex 26



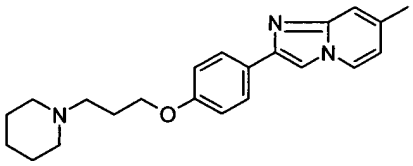

ex 29

Moreover, concerning these aminoalkoxyaryl, it is acknowledged[6] by other groups that "*this privileged pharmacophore has appeared in several other series of H3 receptor ligands*" when referring to the following structures:

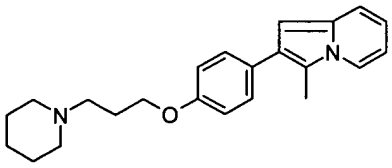
- fluorene oxime bearing a piperidinoethoxy appendage[14]




- phenylimidazopyridine bearing a piperidinopropoxy appendage[15]




- phenylindolizine bearing a piperidinopropoxy appendage[10]

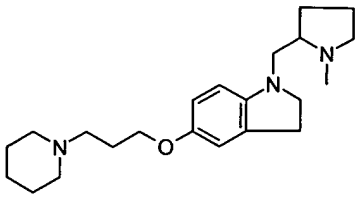



[14] P.C. Ting et al., Bioorg. Med. Chem. Lett. (2002) 12 2643.
[15] C. Shah et al., Bioorg. Med. Chem. Lett. (2002) 12 3309.



remarks

- indoline bearing a piperidinopropoxy appendage[16]



Thus, even other groups recognise that formula (IIa) of the present application is a good blueprint to build H3 ligands with a large diversity brought onto that scaffold.

Note that a close analysis has been published in a more detailed manner in a very recent review made by one of said groups[17].

In summary, as suggested by the Supervisor, Applicants have now directed the claims to cover subject matter of the disclosed examples which have the H3 receptor activity as discussed above, and thus the invention as presently claimed is clearly enabled to one skilled in the art by the present specification. Accordingly, the Examiner's rejection under 35 U.S.C. §112, insofar as applied to the claims as amended, is respectfully traversed and should be withdrawn.

In light of the amendments and arguments as set forth above, and the information provided herewith. Applicants submit that the present application has now been placed in condition for allowance, and such action is earnestly solicited.

**END OF REMARKS**

[16] WO 2004/026893.
[17] M. Cowart et al., MiniRev. Med. Chem.( 2004) 4 979-992.